The management of intraocular retinoblastoma has changed dramatically over the past century, and as a result, so have the outcomes in terms of saving the lives, eyes, and vision of our patients. Retinoblastoma was almost universally fatal a little more than 100 years ago, but now in the Western world it has the highest cure rate of any pediatric solid tumor.1

How did we get from there to here? Treatment algorithms for retinoblastoma advanced periodically during the 20th century, and as a result, outcomes in terms of survival and the preservation of eyes and vision steadily improved. Now in the first decade of the 21st century, an emerging treatment paradigm promises to further revolutionize the management of the disease worldwide. This article reviews the path to where we are today and the potential of this new treatment approach to preserve our patients’ vision and improve their quality of life.

TOWARD SIGHT PRESERVATION

In the late 1800s and early 1900s, there were few survivors of retinoblastoma. The only treatment was enucleation, and usually the tumor was diagnosed at a stage at which removing the eye did not save the patient’s life. With enucleation, the survival rate was perhaps 5% at the turn of the 20th century.

Successful treatment of retinoblastoma with radiation was first reported in 1903.2 (X-rays were used therapeutically for cancer treatment within a year of their discovery by Roentgen in 1895, and for retinoblastoma only a few years later.) From that time until the 1940s, the use of radiation became more and more common.

And it cured the cancer; retinoblastoma was, and still is, one of only a few malignancies in children that can be cured by radiation alone. But although more patients now survived as techniques and dosages for radiation were refined, and some kept their eyes, none retained vision.

In England in the 1930s, Stallard3 introduced radioactive plaques that allowed radiation to be delivered to only a portion of the eye without irradiating the whole eye and orbit. In the 1940s, Reese and colleagues4 in New York devised methods to deliver external radiation that saved eyes and preserved vision. These developments were accompanied by a dramatic change in treatment philosophy. The standard protocol until that time was to remove the worse eye surgically and treat the less involved eye with radiation. Now, more patients survived and kept their eyes, and in some cases, their vision.

In the 1950s, Meyer-Schwickerath5 in Germany introduced the concept of photocoagulation with white light to destroy small tumors. It was soon recognized that occasionally retinoblastoma could be treated with photocoagulation alone, without enucleation or radiation, and that this could preserve eyes with some vision.

In the 1960s, Lincoff6 introduced the use of cryotherapy, which, like photocoagulation, was successful in destroying small tumors and preserving vision in some eyes.

CHEMOTHERAPY

Until the late 1980s, these were the tools available for treatment of retinoblastoma, and with these tools, by that time, the survival rate for retinoblastoma in the Western world exceeded 90%. (It is a sad but well-documented fact that, worldwide, the majority of children with retinoblastoma still die, even in 2010.)

As survival improved in patients treated with radiation, however, clinicians began to recognize that in the long term, these patients often developed second nonocular cancers in the irradiated field.7 In addition, as genetic testing became possible, it was noted that second (and third, and fourth) tumors were more common in patients with the RB1 gene mutation.8

Because these secondary cancers occurred at a rate of 0.5 to 1% per year, and because half of the children who developed these other cancers died, by the 1990s, the most common cause of death in retinoblastoma patients was not the retinoblastoma itself but secondary cancers related to the patients’ genetics or to their radiation treatment.8
As clinicians began to look for alternatives to radiation—not because it did not work but because of these long-term complications—the use of systemic chemotherapy was widely adopted. Systemic chemotherapy for retinoblastoma was first described by Kupfer in the 1950s, but interest grew starting in the 1990s, and there are now more than 150 publications on the subject. These publications have shown that three cycles of carboplatin-based chemotherapy over 3 months can reduce the size of tumors by almost 50%.

Unfortunately, chemotherapy alone rarely cured the tumors, but if they were reduced to a small enough size, they could be treated with laser, cryo, plaques, or external radiation. With these adjunctive treatments, the success rate of systemic chemotherapy was comparable to radiation but without the radiation-related side effects.

**DISENCHANTMENT**

So the good news about systemic chemotherapy was that it worked against retinoblastoma, and it has worked in many investigators’ hands—leading to the aforementioned 150-plus publications on the subject. The bad news was that, alone, it did not cure cancer, so nearly all patients needed additional treatment with radiation, plaque, laser, cryo, or even enucleation. This greatly increased the amount of time necessary to treat and cure patients, and the costs, both economic and in increased burdens, on families.

But there are other problems with systemic chemotherapy for retinoblastoma as well, which have resulted in widespread disenchantment with this approach. One side effect of chemotherapy in these children has been hearing loss, which is, of course, unfortunate in children who already have vision problems; rates of 5 to 33% permanent hearing loss after chemotherapy have been reported. In one report from Mexico, where cisplatin was used, 100% of children experienced permanent hearing loss.

In addition, common complications of chemotherapy include the need for transfusions and ports and the occurrence of febrile neutropenia. Toxicities, including second cancers, can result from the chemotherapy as well. Multiple studies have found that children receiving chemotherapy and radiation are at higher risk for development of second cancers than those receiving radiation alone. Secondary acute myelocytic anemia, a virulent form of leukemia that is difficult to treat and has a high mortality rate, has been reported after chemotherapy in 15 children with retinoblastoma and is now the most common second cancer in some countries.

**SUPERSELECTIVE CHEMOTHERAPY**

Because of these issues with systemic chemotherapy for retinoblastoma, clinicians have sought more selective (less toxic) ways of treating it. At Memorial Sloan-Kettering Cancer Center in New York several years ago, we began to investigate a technique we call superselective ophthalmic artery chemotherapy. Beginning in 2006 as an institutional review board-approved experimental protocol, the technique was so successful that it has now replaced systemic chemotherapy at our center for all children over the age of 3 months. It has completely replaced radiation; we have not used primary radiation in any child in the past 4.5 years. This intraarterial mode of treatment is more effective, faster, easier on child and family, less expensive, and less toxic than any other treatment modality available. It has now been taught and performed in 20 countries worldwide.

In the intraarterial technique, a catheter is inserted into the femoral artery on an outpatient basis with the child under general anesthesia, passed through the abdominal and thoracic aorta into the internal carotid artery, and then placed directly in the ophthalmic artery, the only blood vessel supplying the eye. A tiny volume of a chemotherapeutic agent or agents—between 0.5 and 1 cc depending on the size of the child—is infused over the course of 30 minutes.

Our most recent publication reported our 3-year experience with 23 newly diagnosed patients with retinoblastoma treated with 75 separate intraarterial chemotherapy infusions. Cannulation of one or both ophthalmic arteries (five patients had bilateral disease) was achieved in all eyes (Figure 1). All children survived, and only one proceeded to enucleation for progression of disease. No patient required transfusion or hospitalization, no febrile neutropenia was seen, and ocular complications included only transient forehead hyperemia, lid edema, and loss of lashes.

**IMPLICATIONS**

We have now performed this procedure more than 300 times. For the first time, primary chemotherapy
alone has cured a solid cancer in children (except for germ cell tumors and choriocarcinoma); 40% of our children have received only superselective chemotherapy, and 90% have retained the eye, many with useful vision.

Superselective ophthalmic artery delivery is a way of increasing the chemotherapy dose to the tumor and decreasing it to the body. While we do not know the exact intraocular concentration of the chemotherapy drug, we know it is in excess of 100 times the concentration that would kill a human if administered at the same concentration systemically. But these children do not get sick because the dose to the body is so small; they do not lose their hair or their appetites. Extensive evaluation has shown that the treatment is not toxic to the eye if the eye has not previously been treated with systemic chemotherapy and/or radiation. In fact, in some children who have no vision before infusion, the retina settles down and vision is achieved.

This treatment works in the eye because at the time of diagnosis, retinoblastoma is localized to the eye. The rest of the body does not need chemotherapy, which unfortunately is not true in many cancers. It also works in the eye because the doses and the drugs we use are effective and not toxic. Retinoblastoma is very sensitive to chemo, but in the conventional doses used systemically, it is not curative.

As a result of our work, a number of centers, including Memorial Sloan-Kettering, are now investigating the use of this approach for other cancers. Memorial recently opened a new center dedicated to this approach for cancer.

The proof of a technique lies in its replication by other centers, and superselective ophthalmic artery chemotherapy is now being done successfully in 20 countries. Not only have our results been replicated; in some cases, reports suggest even better results. Notably, many of these countries are emerging or developing nations. As noted above, although more than 90% of patients with retinoblastoma survive in the Western world, the rate of survival worldwide is less than 50%. It is encouraging that this high-tech procedure, on the cutting edge of treatments for retinoblastoma and potentially other types of cancers, is succeeding in the hands of clinicians in the developing world. I predict that by the end of 2010 or early 2011 this procedure will have been performed in more emerging countries than developed countries.

It has been quite a journey from the turn of the 20th century to the turn of the 21st. With conventional treatments, retinoblastoma has the highest cure rate of any childhood cancer, and we should all be proud of the contributions of researchers and clinicians over the past 100 years to achieve that. At the same time, that achievement makes it a challenge to introduce further improvement.

Experience to date suggests that superselective ophthalmic artery chemotherapy is more effective, faster, and safer than conventional treatments for this cancer, which already had good success rates. Now we can address not only the survival of our patients, but also the quality of their lives, in a way that matters. Like the Wright brothers at the dawn of aviation, I look forward to the future development of this new, transformational approach to cancer.

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